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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/674,228	09/29/2003	Samir M. Hanash	108140.00015	1891

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EXAMINER	
REDDIG, PETER J	
ART UNIT	PAPER NUMBER
1642	

NOTIFICATION DATE	DELIVERY MODE
06/09/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

NYIPDocket@arentfox.com
Patent_Mail@arentfox.com

Office Action Summary	Application No.	Applicant(s)	
	10/674,228	HANASH ET AL.	
	Examiner	Art Unit	
	PETER J. REDDIG	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 February 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/27/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The Amendment filed February 29, 2008 in response to the Office Action of August 27, 2008 is acknowledged and has been entered.

2. Claims 1, 2 and 4 are currently being examined.

3. The following rejections are being maintained:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1, 2, and 4 remain rejected under 35 USC 103(a) for the reasons previously set forth in section, pages 2-6 of the Office Action of August 27, 2008.

Applicants argue that Hirsch et al. is cited for disclosing a method of identifying proteins that induce antibodies in Hodgkin's disease (i.e., lymphoma) by isolating proteins from cancer cells derived from Hodgkin's disease patients and subjecting the isolated proteins to 2D PAGE followed by Western blot analysis with sera from cancer patients as compared to normal control patients. The proteins bound by antibodies present in serum of cancer patients, but not in serum of normal patients, are identified as proteins to which a subject with cancer produces antibodies, and detecting the proteins to which the antibodies in the subject's serum sample have bound using an antibody that is specific for autoantibodies in the subject's serum sample.

Applicants argue that in response to Applicants' previous arguments, the Office Action appears to take the position that Applicants' previously-submitted arguments that Hirsch et al. discounts various bands and spots as mere "background noise" are not correct. The Office Action

indicates that one of skill in the art would conclude that only spots differing between test and control samples represent signal, and that by comparing the results, any "background noise" would be readily discernable.

Applicants argue that the Office Action also takes the position that Hirsch et al. does not teach that any spots unrelated to proteins previously discovered by 1D Western blot are merely "the usual background." However, in response to this contention, Applicants argue that the Office Action has apparently not considered the legend to Figure 1 a-c found at the bottom of page 205. It states: "[a] polypeptide with a molecular weight of 65x 10^3 daltons gave a strong reaction in the one- (B, C) and two-dimensional (A) blots. Additional faint bands and spots reflect the usual background reaction." Applicants are at a loss to understand why this disclosure has not been taken into account in the Office Action.

Applicants' argument has been considered, but has not been found persuasive because, as previously set forth, it is well within the skill of those of ordinary skill in the art to recognize background noise in their experimental work by comparing the results of the test assay with the control assay and the detection of background would not discourage one of skill in the art in the art from performing the prior art method. Additionally, there is no indication in the cited passage that the "Additional faint bands and spots" are of the same MW or PI of the P-65 protein to which the autoantibodies bind, which is readily distinguishableby its strong signal..

Applicants argue that while it is apparent from Hirsch et al. that antibodies were produced for one protein, namely, P-65 in leukemia patients, Hirsch et al. first had to perform 1D PAGE and Western blotting to identify a protein to which only 17% of patients with cancer studied raise antibodies, and to which 2% of controls also have reactive antibodies. This lack of

discrimination leads Hirsch et al. to conclude that "the relationship between antibodies to P-65 and HD is not clear" (p. 207, col. 1, lines 3-4).

Applicants' argument has been considered, but has not been found persuasive. In the cited passage Hirsch et al. is not referring to the identification of the p65 protein to which the autoantibodies bind, but the p65 protein's relationship to Hodgkin's disease, as indicated by the next line on p. 207 that states "It could be speculate that there is a gentic disposition for both, the incidence of HD and antibodies toP-65". Thus there Hirsch et al. does not suggest that there methods lack discrimination.

Applicants argue that one of ordinary skill in the art, having the disclosure of Hirsch et al. before him or her, would conclude that 2D Western blots may only be interpreted by having a priori knowledge of the protein of interest. The presently-claimed invention provides a means, previously not available, for performing 2D Western blots to discover proteins to which patients with cancer raise autoantibodies, where individuals without cancer do not, without prior knowledge of the proteins to be so identified. By not dismissing spots as "the usual background" and by providing a method of directly comparing the protein spots recognized by antibodies from cancer patients and cancer-free controls, the presently-claimed invention provides a method that is the exact opposite of that disclosed in Hirsch et al.

Applicants' argument has been considered, but has not been found persuasive because Applicants are arguing limitations, to discover proteins to which patients with cancer raise autoantibodies, where individuals without cancer do not, without prior knowledge of the proteins to be identified, that are not in the claims. Furthermore, given the conventional nature of using 2-D electrophoresis to identify proteins, one of skill in the art would not need prior knowledge to

use the method of Hirsch et al. to identify proteins without prior knowledge of the proteins. Additionally, it is well within the skill of those of ordinary skill in the art to recognize background noise in their experimental work by comparing the results of the test assay with the control assay, as previously set forth and above.

Applicants argue that Krska et al. is cited for allegedly disclosing a conventional 2-D electrophoresis method for detecting primary antibodies bound to the antigen of interest that are transferred to a membrane. However, without conceding that the combination of Hirsch et al. and Krska et al. is proper, Applicants submit that Krska et al. does not remedy the deficiencies of Hirsch et al. with respect to the presently-claimed invention.

Applicants argue that the Examiner has taken the view that Krska et al. provides further support for a method of 2-dimensional PAGE followed by Western blotting analysis. Applicants have not claimed such a method in isolation and acknowledge that the use of 2D gel separation followed by Western blotting was known to the skilled artisan prior to the date of the current invention. The key difference between the presently-claimed invention and the cited references is that Krska et al. and Hirsch et al. both require a priori knowledge of the protein of interest before the Western blot patterns can be interpreted, whereas the presently claimed invention permits the discovery of proteins without prior knowledge of the proteins to be so identified.

Applicants' argument has been considered, but has not been found persuasive because Applicants are arguing limitations, the discovery of proteins without prior knowledge of the proteins to be identified, that are not in the claims. Furthermore, given the conventional nature of using 2-D electrophoresis to identify proteins, one of skill in the art would not need prior

knowledge to use the combined methods of Hirsch et al. and Krska et al. to identify proteins without prior knowledge of the proteins.

Applicants argue that Krska et al. does not use sera containing antibodies raised against endogenous antigens, but rather uses polyclonal and monoclonal antibodies artificially raised by immunization with the target protein. Even using this approach, Krska et al. teaches the necessity of testing antibodies for their ability to detect the denatured form of the target protein in Western blots (p. 6434, col. 1, line 46 - col. 2, line 1) before they can be used routinely. Using this approach, Krska et al. obtained only 1 out of 700 hybridoma clones with the required characteristics (p. 6435, col. 2, lines 28-37). In reviewing Krska et al., one of ordinary skill in the art would conclude that it was extremely unlikely that the natural presentation of an endogenous protein would elicit an antibody response capable of recognizing the denatured forms of proteins in Western blots. (This position is supported by the attached excerpt from Sambrook et al., Molecular Cloning: A Laboratory Manual, which was submitted in the recent opposition proceedings of the corresponding European application.

Applicants' argument has been considered, but has not been found persuasive because the claims are not drawn to identifying antibodies for routine use. The fact that Krska et al. chose the antibody that best suited their needs does not indicate that none of the other antibodies tested work to some degree and does not obviate the fact that Hirsch et al. using 2-D electrophoresis was able to identify a protein to which a subject with cancer produced autoantibodies, whether it is likely or not. Although it is unclear to which section of Sambrook et al. Applicants are referring, it is noted that Sambrook et al. teaches:

> Although there is an obvious danger that comes from using undefined reagents to assay a target protein that may also be poorly characterized, most problems that arise with western blotting in practice can be solved by designing adequate controls. These include the use of (1) antibodies (i.e., preimmune sera or irrelevant monoclonal antibodies) that should not react with the target protein and (2) control preparations that either contain known amounts of target antigen or lack it altogether, see p. 18.60, 3rd para.

Thus, Sambrook et al. supports the idea that with the proper controls, as Hirsch et al. has, one of skill could predictably make and use the claimed method at the time the invention was made based on the combined methods of Hirsch et al. and Krska et al.

Applicants argue that the Office Action takes the position that one skilled in the art would combine the disclosures of Hirsch et al. and Krska et al. because their combined teachings provide the means and motivation to identify proteins to which a subject with cancer produces antibodies. Applicants argue that it must be understood that developing a Western blot with a serum sample from a cancer patient is very different from using a polyclonal hyperimmune serum from a rabbit, or a hybridoma culture supernatant containing a murine monoclonal antibody. The complexity of the staining pattern in the former case compared to the latter two situations renders interpretation difficult. When faced with such complexity, Hirsch et al. dismissed it as "the usual background staining." In consulting Krska et al., the skilled artisan would expect to see a very clean Western blot result with a single protein being visualized. As clearly demonstrated by the present invention, this is far from the case, and rather than representing "the usual background," the protein spots revealed by the presently-claimed method

allows the identification of important cancer-associated antigens to which patients with cancer mount an antibody response, while subjects without cancer do not.

Applicants' argument has been considered, but has not been found persuasive because background in Western blotting is a well known phenomena in the art and one of normal skill in the art would be readily able to distinguish background from signal as performed by Hirsch et al. Although patients samples may be more complex than a Western blot using a single antibody, this does not obviate the fact that these methods are routine and one of skill in the art could readily perform the claimed methods based on the combined teachings of Hirsch et al. and Krska et al. Even if Hirsch et al. missed some proteins bound by autoantibodies to some proteins spots interpreted as background, this does not obviate the fact that Hirsch et al. identified the p65 protein to which autoantibodies of the Hodgkin's disease patient bind.

Applicants argue that taken together, Hirsch et al. and Krska et al. suggest that the prevalence of antibodies in the serum of cancer patients that react with cellular proteins derived from a host's tumor or representative thereof would be extremely low, if present at all. Furthermore, neither document teaches the identification of proteins to which patients with cancer have mounted a detectable antibody response while those without cancer do not, since even the control group in Hirsch et al. exhibits antibody reactivity to P-65. Applicants argue that thus the skilled artisan would thus lack the means and motivation to arrive at the present invention based on the combination of Hirsch et al. and Krska et al. Applicants argue that taken accordingly, the combination of Hirsch et al. and Krska et al. fails to disclose or suggest all of the features of the claims, and nothing in their disclosures would lead one skilled in the art to

modify them to arrive at the presently-claimed invention without the benefit of hindsight reconstruction based on Applicants' disclosure.

Applicants' argument has been considered, but has not been found persuasive because although the prevalence of antibodies in the serum of cancer patients that react with cellular proteins derived from a host's tumor or representative thereof may be low, Hirsch et al. did identify p65 to which autoantibodies of the Hodgkin's disease patient bound. Additionally, only 1 control serum sample out of 55 control serum samples exhibited binding to P-65 which means 54 controls samples did not exhibit binding when the sample from the Hodgkin's disease patient did., see p. 205, 2nd col. One of skill in the art would not expect that all controls would be negative all of the time and a roughly 2% false positive rate would not discourage one of ordinary skill in the art to combine the methods of Hirsch et al. and Krska et al. to make and use the method as claimed.

Applicant's arguments have not been found persuasive and the rejection is maintained.

5. No claims allowed.

6. This action is a **final rejection** and is intended to close the prosecution of this application. Applicant's reply under 37 CFR 1.113 to this action is limited either to an appeal to the Board of Patent Appeals and Interferences or to an amendment complying with the requirements set forth below.

If applicant should desire to appeal any rejection made by the examiner, a Notice of Appeal must be filed within the period for reply identifying the rejected claim or claims appealed. The Notice of Appeal must be accompanied by the required appeal fee.

If applicant should desire to file an amendment, entry of a proposed amendment after final rejection cannot be made as a matter of right unless it merely cancels claims or complies with a formal requirement made earlier. Amendments touching the merits of the application

which otherwise might not be proper may be admitted upon a showing a good and sufficient reasons why they are necessary and why they were not presented earlier.

A reply under 37 CFR 1.113 to a final rejection must include the appeal form, or cancellation of, each rejected claim. The filing of an amendment after final rejection, whether or not it is entered, does not stop the running of the statutory period for reply to the final rejection unless the examiner holds the claims to be in condition for allowance. Accordingly, if a Notice of Appeal has not been filed properly within the period for reply, or any extension of this period obtained under either 37 CFR 1.136(a) or (b), the application will become abandoned.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter J. Reddig whose telephone number is (571) 272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Peter J Reddig/
Examiner, Art Unit 1642
/P. J. R./

/Karen A Canella/
Primary Examiner, Art Unit 1643